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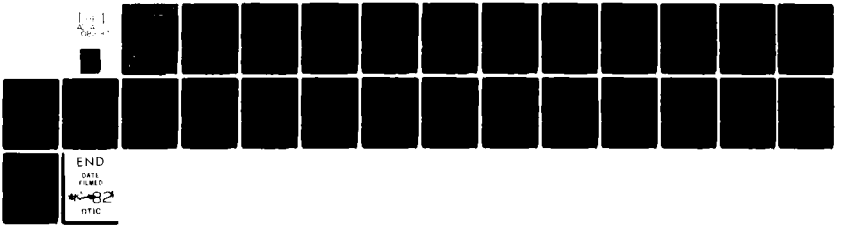

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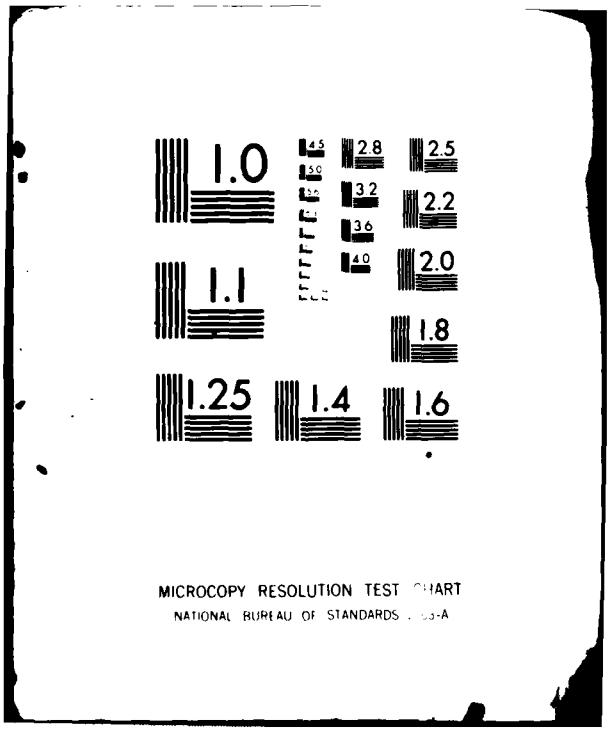
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SEDATIVE-HYPNOTICS AND HUMAN PERFORMANCE

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SEDATIVE-HYPNOTICS AND HUMAN PERFORMANCE

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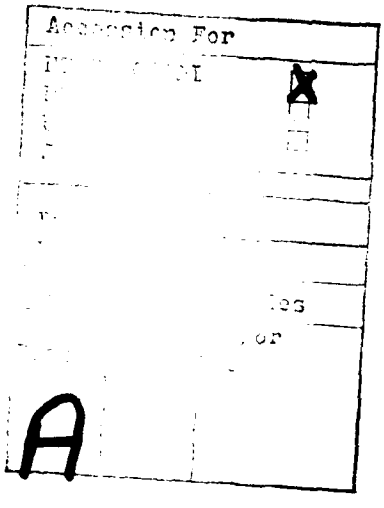

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SUMMARY

Sleep laboratory studies have demonstrated that most sedative-hypnotics increase total sleep time, at least during short-term administration. There is, however, increasing awareness that an hypnotic's effectiveness in inducing and maintaining sleep is not the only relevant question to be asked. Of increasing concern is the "hangover" effect. Does the hypnotic improve or impair awake performance? The 1979 report of the Institute of Medicine (IOM) dealt extensively with the complex problem of assessing hazards and benefits of hypnotics and noted that no documented study has demonstrated a clear relationship between amount of sleep actually obtained by insomniacs and daytime performance. The report discussed the importance of data which demonstrate that many hypnotics continue to influence the nervous system throughout the day following nocturnal administration. The authors of the report also noted that hypnotics may reduce performance and that persons may be unaware of the reduction in their daytime efficiency. The IOM report stressed the need for more data on the effects of hypnotics on daytime performance, not only to determine their safety and side effects but also to determine possible benefits of hypnotic use.

A single study could not be designed to answer all the unresolved questions concerning sleeping pill effects. However, when hypnotic, sleep, and performance studies are examined as a single sample, consistent findings are evident which answer questions that individual studies do not. This review focuses on those studies which used psychoactive drugs to induce sleep and which evaluated performance the next day. To be included, each study had to: (a) evaluate one or more sedative-hypnotics administered before going to bed; (b) administer one or more performance tests 7 to 22.5 hours post-ingestion after 6.5 or more hours of bed time; (c) include a placebo control; (d) use and report the results of statistical analysis; and (e) use compounds that are presently marketed in some country and were used in the study to induce sleep. Fifty-two studies met these criteria. Benzodiazepines were most frequently studied. The major conclusions are as follows:

1. Most sedative-hypnotic and performance studies have used normal, rather than insomniac, subjects. Most of the normal subjects were male.
2. All hypnotics (at some doses) produce decrements in performance the next day after nighttime ingestion.
3. Most performance studies used psychomotor tasks and little consistent data are available on cognitive functioning and more complex human behaviors.
4. Different psychomotor performance tests are differentially sensitive to the effects of sedative-hypnotics; the pattern of sensitivity is similar for all types of sedative-hypnotics.
5. When multiple dose levels of a given drug were examined in a given study, consistent dose differences were found. High doses more consistently show a decrement when compared with placebo performance than lower doses.
6. Long-acting drugs generally show more performance decrement, but half-life data were not consistent.

Our findings clearly indicate that taking any of the currently available sedative-hypnotics will not cause the next day's performance to excel over that when a placebo is taken. Sedative-hypnotics generally improve the quality of sleep, but not the quality of daytime performance. The higher doses are more likely to produce a performance decrement; thus, the physician should determine the lowest possible hypnotic dose for each patient.

INTRODUCTION

Numerous sleep laboratory studies have demonstrated that nearly all prescription sedative-hypnotics increase total sleep time, at least during short-term administration. There is, however, increasing awareness that an hypnotic's effectiveness in inducing and maintaining sleep is not the only relevant question to be asked and may not even be the most important. Of increasing concern is the "hangover" effect. Does the hypnotic improve or impair awake performance? In its 1979 report (Solomon, 1979), the Institute of Medicine (IOM) dealt extensively with the complex problem of assessing hazards and benefits of hypnotic drugs. The panel noted that the risk of not taking a sleeping pill "seems to be chiefly of subjecting the patient to anticipating distress while lying awake at night and/or dysphoria during the day after a poor night's sleep" (Solomon, 1979, p.155). There is also the fear that this loss of sleep will cause impaired performance the next day. Do the data support these assumptions? Based upon its study, the IOM panel noted that no documented study has demonstrated a clear relationship between amount of sleep actually obtained by insomniacs and daytime performance. The panel did find, however, that "there is a growing body of evidence that hypnotics may continue to influence the nervous system throughout the day following nocturnal administration" (Solomon, 1979, p.163), suggesting that hypnotics may reduce performance and persons may be unaware of their reduced efficiency. The IOM report stressed the need for more data on the effects of hypnotics on daytime performance, not only to determine their safety and side effects but also to determine possible benefits of hypnotics. "For example, increased sleep in insomniacs ought to lead to better daytime functioning, although no study ever demonstrated this" (Solomon, 1979, p.160).

The IOM report indicated that more data were needed on normal and insomniac patients where (a) the tests are given at various times of the day with various dose levels, (b) the half-life of the hypnotic is evaluated, and (c) the influence of specific drugs on specific tasks is examined. Another unanswered question is: Do the benzodiazepines and the barbiturates produce similar performance decrements? Bond & Lader (1973) report that benzodiazepines are most likely to impair motor skills, while cognitive tasks are more sensitive to barbiturate hypnotics.

Reflecting the current concern over the effects of psychoactive drugs on performance, and in particular psychomotor performance, two recent reviews have focused on this area. Wittenborn (1979) identified speed of performance as particularly sensitive to the effects of benzodiazepines, but noted that learning and memory are also impaired. Hindmarch (1980) summarized the effects of drugs on components of psychomotor functions including sensory processing, central integration, motor responses, and sensory-motor coordination. Both reviews included sleep and nonsleep studies and did not examine such variables as type of drug, dose level, number of nights of administration, or half-life. Though not an extensive review of performance, Nicholson (1981) has critically reviewed many of the issues in the use of short- and long-acting hypnotics in clinical medicine. Because of the widespread use of the benzodiazepines as anti-anxiety drugs, Kleinknecht & Donaldson (1975) reviewed the effects of diazepam on cognitive and psychomotor performance, while, in an earlier review, McNair (1973) included meprobamate in addition to the benzodiazepines, diazepam and chlordiazepoxide. Only one review (Bixler, Scharf, Leo & Kales, 1975) has looked at the effects of hypnotics on performance the next day following bedtime ingestion, but their review focused on the theoretical and methodological considerations. The authors cited the results from 12 studies, with primary attention given to the description of the tasks.

In some of these reviews, as in the IOM report, the inadequacy of the data reported with respect to such questions as the importance of age, sex, dose level, patients vs. normal subjects, acute vs. multiple dose administration, and the comparison of the sensitivity of crossover vs. parallel designs, was stressed. Kleinknecht & Donaldson (1975), noting that females were the more frequent users of diazepam, found most disconcerting the disproportionate use of males in the 17 studies they reviewed. McNair (1973) appeared to be equally concerned over the frequent use of the crossover design because of possible carry-over effects and the fact that most studies used normal subjects rather than insomniac patients, who are the target population for hypnotic drugs.

A single study cannot possibly answer all the unresolved questions and issues raised by the IOM report and the reviews cited. The examination of more than one or two of these variables would make the study prohibitively complex and demanding. Perhaps by looking at all the hypnotic, sleep and performance studies as a single sample, there will be consistent findings, over studies, that answer questions that individual studies cannot. This review focuses on those studies which used psychoactive drugs to induce sleep and that evaluated performance the next day.

METHODS

Study sample. To be included in this review, each study had to: (a) evaluate one or more sedative-hypnotics administered before going to bed; (b) administer one or more performance tests 7 to 22.5 hours post-ingestion after 6.5 or more hours of bed time; (c) include a placebo control; (d) use and report the results of statistical analysis; and (e) use compounds that are presently marketed in some country and were used in the study to induce sleep. Five studies that involved sleep and performance did not meet all five criteria and were not included. Two studies of geriatric patients, having other medical complaints besides sleep problems, were also not included. Each study was examined for the following variables.

1. Sex of subjects.
2. Age of subjects.
3. Experimental design: crossover vs. parallel groups.
4. Types of populations: normal noninsomniac subjects vs. insomniac patients.
5. Performance tests administered and statistical results.
6. Class of drug administered: barbiturates, benzodiazepines, other hypnotics.
7. Specific drugs.
8. Dose level of each drug.
9. Dosage schedule: number of nights of administration.
10. Hours post-drug of performance testing.
11. Half-life of parent drug and its metabolites.
12. Blood level of drug or metabolite.

Performance tests. A wide variety of performance tests was used, but only those tests that were objectively scorable, e.g., psychomotor, cognitive, memory, perceptual, or attention tasks (including vigilance), were included.

With the exception of critical flicker fusion (CFF), other physiological or psychophysiological measures were seldom recorded and these were not included. For this review, some tasks were combined for tabulation, e.g.:

(a) arithmetic includes addition and serial subtraction; both time and errors were scored

(b) memory includes short-term and long-term, and includes such tasks as word memory, paired associates, and digit span

(c) card sorting includes both decision time and motor functioning, simple and complex

(d) vigilance includes both auditory and visual tasks

(e) coordination includes balance board, stabilometer, and hand-eye coordination

(f) manual dexterity includes a test labeled manual dexterity and the Purdue Pegboard

Simulator tests, such as flight simulators or driving simulators, were not included in the statistical summary, but the results of these simulator studies will be noted.

The primary survey method included a computer search of Index Medicus and a Medlars search of all titles that included hypnotics (all types), sleeping pills (all types), or performances of any kind. These two primary sources were augmented by personal knowledge of work done and reported, and by cross-checking of published references of specific drug studies and review articles. A total of 413 complete articles were screened. Most articles were rejected because no performance tests were administered or they were not sleep studies.

Placebo/drug comparisons. The primary data for this review were the statistical results of the comparison of the performance scores on each task the day following drug administration and those following placebo administration. In computing the number of placebo/drug comparisons, a comparison was tabulated for each drug and for each test. If 3 tests were given and a placebo/drug comparison was made for each of 4 drugs, the test comparisons for that study were 12. If the same study had used two doses and the comparisons had been made after night 1 and night 4, the total number of comparisons for that study would have been 48 (2 doses, times 4 drugs, times 3 tests, times 2 nights). If, however, the same placebo/drug comparisons were made at 7, 11, and 20 hours post-drug, for the overall summary analysis, these three comparisons of the same drug, same dose level, and same task were counted as only one placebo/drug comparison. As will be seen later, the conclusions derived from this overall summary were not changed when repeated testing on the same day was considered in the time post-ingestion analysis. Placebo/drug score comparisons that were significantly different at the 0.05 level or better were recorded as a drug-related increment or decrement. Other comparisons were recorded as no difference between drug and placebo performance. Percent decrements for a task or drug listed in the tables were calculated as the number of comparisons that showed a decrement divided by the total number of placebo/drug comparisons made. Percent increments were not computed because there were only 6 comparisons that showed improved performance. These were in normal subjects with benzodiazepines, and 3 of these were on CFF with clobazam 20 mg (Hindmarch & Parrott, 1978, 1979, 1980a).

In the results section, after a description of the overall characteristics of the studies, the findings for the benzodiazepines will be presented. The variables analyzed included type of subject, task sensitivity, dose level, time post-ingestion, drug analysis, number of nights of administration, and half-life. All of these variables were examined for studies using normal subjects and, where data permitted, for studies using insomniacs. The same analysis, again where data permitted, was then done for studies using barbiturates with both normal and insomniac subjects.

RESULTS

Characteristics of Studies

A total of 52 studies met all five criteria for inclusion. The majority (37, or 71%) of the 52 studies were from European authors and 24 (48%) came from three laboratories (I. Hindmarch, University of Leeds; A. Nicholson, Royal Air Force Institute of Aviation Medicine; and A. Bond & M. Lader, University of London). Thirteen (25%) were from a single laboratory (Hindmarch). No single laboratory so dominated the studies from the United States. T. Roth (Henry Ford Hospital), with 4 publications, and L. Johnson (Naval Health Research Center), with 2, are the only multiple contributors from the United States. M. Linnoila (Duke University) is listed with 3 articles, but 2 of these were submitted when he was in Finland. Though no restriction as to time period was used, all the studies were reported between 1959 and 1981. Ninety-six percent were published in the last decade, and 63% within the last 5 years.

Of the total 834 subjects in the 52 studies, 67% were male and 33% female. These 834 subjects took one or more of the 25 different sedative-hypnotics. As will be seen later, many studies used more than one drug and more than one task; thus, the sum of the studies over drugs exceeds 52. In Table 1 are the breakdowns of all the studies with respect to type of subject, drug, and sex. Normal male subjects, between 18–40, predominated. Among the volunteer subjects, the percent of women varied from 6% for flurazepam studies to 51% for nitrazepam studies. For triazolam, temazepam, and flunitrazepam, the respective percents of female subjects were 7, 16, and 35. None of the studies reported a sex by treatment interaction analysis.

Only 8 of the 52 studies evaluated insomniac patients and, in these studies, both sexes were equally involved. The age of the insomniac subjects varied between 10 and "69 plus" (Castleden, George, Marcer & Hallett, 1977). In only one of the studies (Castleden *et al.*, 1977) was a comparison made to evaluate the interaction of drug and age on performance. Due to the fact that many studies reported only age ranges, we could not do an age analysis.

TABLE 1
Characteristics of Studies

Drugs	Number	Studies	Test Comparisons	Subjects	Percent Male	Percent Female
Normal Subjects						
Benzodiazepines	11	37	270	652	69	31
Barbiturates	7	23	97	301	82	18
Other Hypnotics	7	7	19	156	82	18
Insomniac Subjects						
Benzodiazepines	5	8	66	123	50	50
Barbiturates	2	4	20	55	38	62
Other Hypnotics	None					
Experimental Design						
Crossover	41 (79%)					
Parallel	11 (21%)					

Eleven benzodiazepines were used: clobazam, diazepam, flunitrazepam, flurazepam, lorazepam, lormetazepam, nitrazepam, nordiazepam, oxazepam, temazepam, and triazolam. The seven barbiturates were amobarbital/secobarbital, amylobarbitone, butobarbitone, quinalbarbitone, secobarbital, heptabarbitone, and pentobarbitone. The seven other sedative-hypnotics were chloral hydrate, glutethimide, dichloralphenazone, ecthlorvynol, methaqualone, zobiclone, and methaqualone combined with diphenhydramine.

Experimental design. A majority of the 52 studies, 41 (79%), used a crossover design. Only 37 had a washout period of 3 or more days between drugs or drug and placebo. One study (Allnutt & O'Connor, 1971) reported a single day between drugs, one (Kornetsky, Vates & Kessler, 1959) reported the washout period varied, and for five studies (Malpas, Legg & Scott, 1974; Saario, Linnoila & Maki, 1975; Saario & Linnoila, 1976; Salkind & Silverstone, 1975; Veldkamp, Straw, Metzler & Demissianos, 1974), no washout period was reported.

The question as to which design is more likely to reveal performance decrements cannot be resolved by our data. For the benzodiazepine studies with normal subjects, 30% of the placebo/drug comparisons showed a decrement using crossover designs in contrast to 19% for the parallel design. However, in studies using insomniacs, the percent decrement was 22% for the parallel design and 15% for the crossover design. There were insufficient data for an analysis of the two designs in barbiturate studies.

Benzodiazepines: Normal Subjects

Sensitivity of performance tasks. There were 15 different tasks or groupings of tasks given in one or more of 37 benzodiazepine studies, for a total of 270 placebo/drug comparisons. The 15 tasks tabulated were used with 3 or more drugs (range 3–7), and the placebo/drug comparisons for specific tasks ranged from 6, rotary pursuit, to 44, choice reaction time. The mean number of comparisons per task was 18. The tests are listed in Table 2 in order of largest percent decrement. The data in Table 2 reflect sensitivity without reference to type of sedative-hypnotic, dose level, or time post-ingestion. These variables are, of course, important and will be examined separately. Out of the 270 test comparisons, 78 (28.9%) showed a significant decrement the next day. Because of the small number of comparisons and the limited number of studies, 3 tasks were not included in the tabulation. These tasks were flow spiral maze, one comparison (Bond & Lader, 1972), handgrip, one comparison (Lahtinen, Lahtinen & Pekkola, 1978), and a measure of attention and information processing (Saario *et al.*, 1975; Saario & Linnoila, 1976).

Card sorting, tapping rate, symbol copying, and digit symbol substitution test (DSST) were the 4 most sensitive tasks. The 4 tests with the lowest percent decrement were coordination, CFF, rotary pursuit, and Purdue Pegboard/Manual Dexterity. There was no decrement in coordination, in 12 comparisons with 5 drugs.

Memory included both short- and long-term memory tasks. Four of the 6 decrements occurred in measures of long-term memory (Bixler, Scharf, Soldatos, Mitsky & Kales, 1979; Roth, Hartse, Saab, Piccione & Kramer, 1980a). The short-term memory decrements occurred for a task learned and recalled in the morning following bedtime ingestion of nitrazepam, 10 mg (Adams, 1974; Peck, Bye & Claridge, 1977).

TABLE 2

Benzodiazepine Effects on Performance in Normal Subjects

Test	No. of Benzodiazepines Tested	No. of Test Comparisons	Decrements		References
			Number	Percent	
Card Sorting	5	18	11	61	Bond & Lader (1972, 1973, 1975); Malpas *et al.* (1970); Oswald *et al.* (1979); Roth *et al.* (1977); Veldkamp *et al.* (1974)
Symbol Copying	3	8	4	50	Bond & Lader (1973, 1975); Roth *et al.* (1979)
Tapping Rate	3	13	6	46	Bond & Lader (1972, 1973, 1975); Peck *et al.* (1976, 1977); Walters & Lader (1971)
DSST	6	31	13	42	Bond & Lader (1972, 1973, 1975); Oswald *et al.* (1979); Peck *et al.* (1976, 1977); Roth *et al.* (1977, 1979, 1980b); Veldkamp *et al.* (1974); Walters & Lader (1971)
Memory	6	17	6	35	Adams (1974); Bixler *et al.* (1979); Peck *et al.* (1977); Roth *et al.* (1979, 1980a, b)
Arithmetic	6	20	7	35	Allnutt & O'Connor (1971); Bond & Lader (1972); Hindmarch (1977); Hindmarch & Clyde (1980); Hindmarch & Parrott (1979); Hindmarch *et al.* (1980); Roth *et al.* (1977)
Vigilance	3	9	3	33	Allnutt & O'Connor (1971); Oswald *et al.* (1979); Peck *et al.* (1976, 1977)
Tracking Task	8	17	5	29	Borland & Nicholson (1975, 1977); Clarke & Nicholson (1978); Nicholson & Stone (1980)
Cancellation Task	3	11	3	27	Bond & Lader (1972, 1973, 1975); Castleden *et al.* (1977); Wickstrøm & Giercksky (1980)
Choice Reaction Time	7	44	10	23	Bond & Lader (1973); Clarke & Nicholson (1978); Hindmarch (1976, 1977, 1979a); Hindmarch & Clyde (1980); Hindmarch & Parrott (1978, 1979, 1980a, b); Hindmarch *et al.* (1977a, b, 1980); Pishkin *et al.* (1980); Saario *et al.* (1975); Saario & Linnoila (1976)
Simple Reaction Time	4	22	5	23	Bond & Lader (1972, 1973, 1975); Borland & Nicholson (1975); Hablitz & Borda (1973); Lahtinen *et al.* (1978); Peck *et al.* (1977); Pishkin *et al.* (1980); Roth *et al.* (1979); Walters & Lader (1971)
Purdue Pegboard/ Manual Dexterity	4	11	2	18	Oswald *et al.* (1979); Roth *et al.* (1977, 1979)
Rotary Pursuit	3	6	1	17	Pishkin *et al.* (1980); Roth *et al.* (1977)
Critical Flicker Fusion	6	31	2	6	Hindmarch (1976, 1977, 1979a); Hindmarch & Clyde (1980); Hindmarch & Parrott (1979, 1980a, b); Hindmarch *et al.* (1980)
Coordination	4	12	0	0	Hindmarch (1979a); Roth *et al.* (1979, 1980b); Saario *et al.* (1975); Saario & Linnoila (1976)
TOTAL		270	78	29	

Six of the 7 arithmetic decrements were found by Hindmarch with the serial subtraction test (Hindmarch, 1976, 1977; Hindmarch, Parrott, Hickey & Clyde, 1980). Three of these decrements were increased time to complete subtraction (Hindmarch, 1976, 1977). The other arithmetic decrement occurred on a 15-minute continuous addition task (Roth, Kramer & Lutz, 1977).

With the removal of clobazam, diazepam, and lorazepam (drugs not marketed as sedative-hypnotics), the overall percent decrement is 30.9% and the order of sensitivity remains the same. If the 4 drugs that were used in only one study, oxazepam (Clarke & Nicholson, 1978), lormetazepam (Oswald, Adam, Borrow & Idzikowski, 1979), lorazepam (Roth *et al.*, 1980a), and nordiazepam (Clarke & Nicholson, 1978), are removed, there is still no difference in the 4 most and 4 least sensitive tests.

Dose level. The pattern of increasing decrement with higher dose level is clear for all the drugs reported at more than one dose level except clobazam (Table 3). Hindmarch *et al.* reported all the studies of clobazam. Hindmarch & Parrott (1980b) found a decrement on choice reaction time at 20 mg, but not at any other dose level, and, in their report, they note that their finding in this study is inconsistent with previous work in their laboratory. There appears to be less of a decrement with 60 mg than 40 mg of temazepam, but these temazepam data are based upon only one study (Hindmarch *et al.*, 1980) and the authors are skeptical of their results.

Time Post-ingestion

Task analysis. The placebo/drug task comparisons were examined for 3 time periods post-ingestion: 7–10, 11–14, 15–22.5 hours. These time periods were chosen to bracket the early morning, midday, and evening testing times. The largest percent decrement (34%) occurred in the 11–14 hour post-ingestion period. The 7–10 hour post-ingestion percent decrement was 27%, and that for the 15–22.5 hour time period was 22%. Only choice reaction time, tracking, and arithmetic tasks showed their higher percent decrement in the morning. These results are listed in Table 4. Not unexpectedly, since the data in Table 2 include the results in Table 4, the tasks showing the largest decrement over all 3 time periods were card sorting, symbol copying, tapping rate, and DSST.

Analysis by drugs. For 4 of the drugs, placebo/drug comparisons had been made at all 3 time periods, though only 2 comparisons were made for temazepam and triazolam at some time periods.

The data in Table 5 indicate that, at clinical dose levels, nitrazepam 10 mg and flurazepam 30 mg showed the largest percent decrement, and the decrement for both drugs was consistent over the 3 time periods. It was at the lower dose level for these 2 drugs, and for triazolam 0.5 mg, that the larger percent decrement occurred during the middle testing period. Temazepam had no decrement at any time period with a 20 mg dose and a 13% decrement was present only in early morning testing when 30 mg was given.

Multiple Nights of Administration and Performance

In 13 of the 37 studies, the drug was given for more than one night. In 3 studies (Roth, Hartse, Zorick & Kaffeman, 1980b; Roth *et al.*, 1977; Roth, Piccione, Salis & Kramer, 1979), the drug was given on 2 nights but testing was done only after the second drug night. Seven of the studies on repeated administration were conducted by Hindmarch and his colleagues, using a 4-night

TABLE 3

Benzodiazepines Dose Level and Performance in Normal Subjects

Benzodiazepine	Dose (mg)	No. of Test Comparisons	Decrements		References
			Number	Percent	
Clobazam	10	2	0	0	Hindmarch & Parrott (1980a)
	20	14	3	21	Hindmarch (1979a); Hindmarch *et al.* (1977a); Hindmarch & Parrott (1978, 1980a, b)
	30	7	0	0	Hindmarch & Parrott (1978, 1979)
	40	4	0	0	Hindmarch & Parrott (1978)
Diazepam	5	2	0	0	Clarke & Nicholson (1978)
	10	2	0	0	Clarke & Nicholson (1978)
	15	1	1	100	Borland & Nicholson (1977)
Flunitrazepam	0.25	1	0	0	Nicholson & Stone (1980)
	0.5	1	0	0	Nicholson & Stone (1980)
	1	11	4	36	Bond & Lader (1975); Hindmarch (1977); Hindmarch *et al.* (1977b)
	2	8	4	50	Bixler *et al.* (1979); Bond & Lader (1975); Wickstrøm & Giercksky (1980)
Flurazepam	15	25	2	8	Bond & Lader (1973); Hindmarch (1977); Roth *et al.* (1977, 1979, 1980b)
	30	38	17	45	Bond & Lader (1973); Borland & Nicholson (1975); Hablitz & Borda (1973); Oswald *et al.* (1979); Pishkin *et al.* (1980); Roth *et al.* (1977, 1979, 1980a, b); Saario & Linnoila (1976); Veldkamp *et al.* (1974); Wickstrøm & Giercksky (1980)
Nitrazepam	2.5	7	0	0	Hindmarch & Parrott (1980a); Peck *et al.* (1977)
	5	38	8	21	Adams (1974); Allnutt & O'Connor (1971); Bond & Lader (1972); Hindmarch (1977, 1979a); Hindmarch & Parrott (1980a, b); Lahtinen *et al.* (1978); Malpas *et al.* (1970); Peck *et al.* (1976, 1977); Walters & Lader (1971); Wickstrøm & Giercksky (1980)
	10	35	24	69	Adams (1974); Bond & Lader (1972); Borland & Nicholson (1975); Castleden *et al.* (1977); Hindmarch & Clyde (1980); Lahtinen *et al.* (1978); Malpas *et al.* (1970); Peck *et al.* (1976, 1977); Saario *et al.* (1975); Walters & Lader (1971)
Oxazepam	15	1	0	0	Clarke & Nicholson (1978)
	30	1	0	0	Clarke & Nicholson (1978)
	45	1	1	100	Clarke & Nicholson (1978)
Temazepam	10	4	0	0	Clarke & Nicholson (1978); Hindmarch (1976)
	15	9	0	0	Roth *et al.* (1979, 1980b)
	20	4	0	0	Clarke & Nicholson (1978); Hindmarch (1976)
	30	16	2	13	Clarke & Nicholson (1978); Hindmarch (1976); Pishkin *et al.* (1980); Roth *et al.* (1979, 1980b)
	40	6	3	50	Hindmarch *et al.* (1980)
	60	6	2	33	Hindmarch *et al.* (1980)
Triazolam	0.25	6	0	0	Nicholson & Stone (1980); Roth *et al.* (1977)
	0.5	15	5	33	Hindmarch & Clyde (1980); Nicholson & Stone (1980); Roth *et al.* (1977, 1980a); Veldkamp *et al.* 1974)
	1	2	2	100	Veldkamp *et al.* (1974)

TABLE 4

Analysis by Tasks of Time Post-Benzodiazepine Ingestion and Performance in Normal Subjects

	Hours Post-Ingestion								
	7–10			11–14			15–22.5		
Task	No. of Decrements	No. of Test Comparisons	%	No. of Decrements	No. of Test Comparisons	%	No. of Decrements	No. of Test Comparisons	%
Tapping Rate	2	5	40	4	8	50	3	6	50
Card Sorting	4	10	40	8	14	57	5	16	31
Arithmetic	7	18	39	0	3	0	0	6	0
DSST	8	23	35	6	14	43	4	20	20
Tracking	5	15	33	3	15	20	3	13	23
Vigilance	2	7	29	1	6	17	2	6	33
Simple Reaction Time	4	14	29	3	10	30	2	10	20
Choice Reaction Time	10	40	25	0	9	0	0	8	0
Purdue Pegboard/ Manual Dexterity	2	11	18	1	3	33	2	11	18
Coordination	0	12	0	0	2	0	0	4	0
Symbol Copying	0	4	0	4	4	100	4	8	50
Cancellation	0	3	0	3	8	38	0	4	0
TOTAL	44	162	27	33	96	34	25	112	22

TABLE 5

Analysis by Drugs of Time Post-Benzodiazepine Ingestion and Performance in Normal Subjects

		Hours Post-Ingestion								
		7–10			11–14			15–22.5		
Drug		No. of Decrements	No. of Test Comparisons	%	No. of Decrements	No. of Test Comparisons	%	No. of Decrements	No. of Test Comparisons	%
Flurazepam	15 mg	0	17	0	2	7	29	1	18	6
	30 mg	15	31	48	8	18	44	10	26	38
Nitrazepam	5 mg	3	25	12	4	14	29	1	6	17
	10 mg	15	21	71	12	19	63	4	6	67
Temazepam	20 mg	0	4	0	0	2	0	0	2	0
	30 mg	2	16	13	0	2	0	0	8	0
Triazolam	0.5 mg	3	14	21	1	2	50	1	7	14
	1.0 mg	2	2	100	0	2	0	2	2	100

study design (Hindmarch, 1976, 1977; Hindmarch & Clyde, 1980; Hindmarch & Parrott, 1978, 1979; Hindmarch, Parrott & Arenillas, 1977b; Hindmarch *et al.*, 1980), two multiple-dose studies were reported by Saario and his group (Saario *et al.*, 1975; Saario & Linnoila, 1976), and one by Oswald *et al.* (1979).

Hindmarch and his group have worked mostly with clobazam and temazepam, but also reported one study using nitrazepam, triazolam, and flunitrazepam (Hindmarch, 1977). Hindmarch reported no build-up effect over the 4 nights in any of his studies and, more often, reported an improvement over days after finding a decrement after the initial dose. Saario *et al.* (1975) and Saario & Linnoila (1976) reported no build-up effect over 14 days for either flurazepam 30 mg (Saario & Linnoila, 1976), or nitrazepam 10 mg (Saario *et al.*, 1975), even though there was an increase in serum level of nitrazepam and of the active metabolite of flurazepam, especially during the first 7–10 days. Oswald *et al.* (1979) was the only group that reported a consistent pattern of increasing impairment over a 3-week period with flurazepam 30 mg. The tasks were card sorting, DSST, auditory vigilance, and manual dexterity.

Half-life

Half-life did not adequately explain performance decrements since, across dose levels, flurazepam with its long half-life metabolite (24–100 hours) produced less of a decrement than nitrazepam with a half-life of 18–34 hours. Triazolam, with a half-life of 3–5 hours, produced more of a decrement than temazepam (half-life of 4–10 hours). The above comparisons do not assume that they are comparable dose levels, i.e., that flurazepam 30 mg is comparable to nitrazepam 10 mg.

Benzodiazepines: Insomniac Patients

Sensitivity of performance tasks. As seen in Table 1, benzodiazepines were administered to insomniacs in only 8 studies. Five benzodiazepines were administered: flurazepam (Church & Johnson, 1979; Linnoila, Erwin & Logue, 1980; Salkind & Silverstone, 1975; Vogel, Barker, Gibbons & Thurmond, 1976), N-desmethyl-diazepam (Tansella, Zimmermann-Tansella & Lader, 1974), nitrazepam (Hindmarch, 1979b; Malpas *et al.*, 1974), temazepam (Hindmarch, 1979b), and triazolam (Spinweber & Johnson, in press; Vogel *et al.*, 1976).

The tests used with insomniac patients were the same as those used with normals, listed in Table 2. Of the 66 placebo/drug comparisons made, 12 (18%) showed a decrement. No comparison showed a significant increment in performance. The most sensitive task was choice reaction time 33% decrement, followed by memory 20%, DSST 18%, tapping 17%, and sorting 14%.

Analysis by drugs. Though the number of comparisons for each drug was small (except for flurazepam 30 mg), the data for drugs given at more than one dose level are presented in Table 6 to show the increasing decrement with dose level for those drugs that showed any decrement.

Multiple nights of administration. None of the studies with insomniacs made placebo/drug test comparisons over the 3 time periods. In five of the seven studies, drugs were given over multiple nights with a range of 4 to 14 nights. Two studies gave flurazepam 30 mg. One (Church & Johnson, 1979) found a build-up of effect on choice reaction time over 10 days. In this same study, performance on the DSST was impaired during the first 3 days but was back to baseline by

TABLE 6

Benzodiazepines Dose Level and Performance in Insomniacs

Benzodiazepine	Dose (mg)	No. of Test Comparisons	Decrements		References
			Number	Percent	
Flurazepam	15	3	0	0	Salkind & Silverstone (1975)
	30	23	6	26	Church & Johnson (1979); Linnoila *et al.* (1980); Salkind & Silverstone (1975); Vogel *et al.* (1976)
Nitrazepam	5	4	0	0	Hindmarch (1979b); Malpas *et al.* (1974)
	10	2	0	0	Malpas *et al.* (1974)
Nordiazepam	10	10	1	10	Tansella *et al.* (1974)
	20	10	2	20	Tansella *et al.* (1974)
Temazepam	15	2	0	0	Hindmarch (1979b)
	20	2	0	0	Hindmarch (1979b)
	30	2	2	100	Hindmarch (1979b)

the 10th day. In contrast, in a 14-day flurazepam 30 mg study (Linnoila *et al.*, 1980), no decrement was found at the beginning, middle, or end of the study on simple reaction time, tracking, visual vigilance, or a continuous performance test. Linnoila *et al.* reported a negative relationship between errors on the tracking test and the serum level of the flurazepam metabolite, N-desalkyl-flurazepam. In two studies (Spinweber & Johnson, in press; Vogel *et al.*, 1976), triazolam 0.5 mg was administered. In neither study was there a build-up effect. The other three studies (Malpas *et al.*, 1974; Salkind & Silverstone, 1975; Tansella *et al.*, 1974) did not evaluate the possible build-up effect as testing was done only at the end of the treatment period.

Barbiturates: Normal Subjects

Sensitivity of performance tasks. As listed in Table 1, 7 barbiturates were administered to 301 patients in 23 studies. The same tasks listed in Table 2 were given in the barbiturate studies. Sensitivity of the 15 tasks is shown in Table 7. A total of 97 placebo/barbiturate comparisons were made, and in 29 (29.9%) of these the drug produced an impairment. The 4 most sensitive tasks, in order of sensitivity, were tracking, cancellation, DSST, and sorting. The 4 least sensitive tasks were rotary pursuit, Purdue Pegboard/Manual Dexterity, arithmetic, and choice reaction time. Due to the small number of comparisons for many of these tasks, these results can be, at most, suggestive.

Dose level. Four of the 7 barbiturates had been given at more than one dose level. The relation of dose level to performance decrement is shown in Table 8. Except for heptabarbitone (with only one test), there is a larger percent decrement with higher doses.

Time post-ingestion. The small number of tasks given at the 3 time periods indicate these data must be viewed with caution, but the pattern over the 3 time periods is similar to that for benzodiazepines. For the 7–11 hour period, there was a decrement of 30% (9/30), at 11–14 hours it was 34% (11/32), and at 15–22.5 hours the percent decrement was 23% (6/21). The number of placebo/drug comparisons were so few that it was not possible to examine post-ingestion time for specific barbiturates.

TABLE 7

Barbiturate Effects on Performance in Normal Subjects

Test	No. of Barbiturates Tested	No. of Test Comparisons	Decrements		References
			Number	Percent	
Tracking	3	6	5	83	Borland & Nicholson (1974, 1975); Borland *et al.* (1975); Kaplan *et al.* (1968)
Cancellation Task	2	4	2	50	Bond & Lader (1972, 1973); Zimmermann-Tansella *et al.* (1976)
DSST	4	15	7	47	Bond & Lader (1972, 1973); Kornetsky *et al.* (1959); Peck *et al.* (1976); Roth *et al.* (1977, 1979, 1980b); Walters & Lader (1971); Zimmermann-Tansella *et al.* (1976)
Card Sorting	3	7	3	43	Bond & Lader (1972, 1973); Malpas *et al.* (1970); Roth *et al.* (1977); Zimmermann-Tansella *et al.* (1976)
Simple Reaction Time	5	11	4	36	Bond & Lader (1972, 1973); Borland & Nicholson (1975); Borland *et al.* (1975); Pishkin *et al.* (1980); Roth *et al.* (1979); Walters & Lader (1971); Zimmermann-Tansella *et al.* (1976)
Critical Flicker Fusion	1	3	1	33	Hindmarch (1979a); Hindmarch & Parrott (1980b)
Vigilance	2	3	1	33	Allnutt & O'Connor (1971); Peck *et al.* (1976)
Tapping Rate	3	10	3	30	Bond & Lader (1972, 1973); Kornetsky *et al.* (1959); Peck *et al.* (1976); Walters & Lader (1971); Zimmermann-Tansella *et al.* (1976)
Symbol Copying	4	6	1	17	Bond & Lader (1973); Kornetsky *et al.* (1959); Roth *et al.* (1979); Zimmermann-Tansella *et al.* (1976)
Coordination	3	6	1	17	Hindmarch (1979a); Roth *et al.* (1979, 1980b); Saario & Linnoila (1976)
Memory	3	7	1	14	Adams (1974); Bixler *et al.* (1979); Roth *et al.* (1979, 1980b)
Choice Reaction Time	3	8	0	0	Bond & Lader (1973); Hindmarch (1979a); Hindmarch & Parrott (1980b); Hindmarch *et al.* (1977b); Pishkin *et al.* (1980); Saario & Linnoila (1976); Zimmermann-Tansella *et al.* (1976)
Arithmetic	3	5	0	0	Allnutt & O'Connor (1971); Bond & Lader (1972); Roth *et al.* (1977); Zimmermann-Tansella *et al.* (1976)
Purdue Pegboard	3	3	0	0	Roth *et al.* (1977, 1979)
Rotary Pursuit	2	3	0	0	Pishkin *et al.* (1980); Roth *et al.* (1977); Siegler *et al.* (1966)
TOTAL		97	29	30	

TABLE 8

Barbiturates Dose Level and Performance in Normal Subjects

Barbiturate	Dose (mg)	No. of Test Comparisons	Decrements		References
			Number	Percent	
Amylobarbitone	100	21	3	14	Hindmarch (1979a); Hindmarch & Parrott (1980b); Hindmarch *et al.* (1977b); Malpas *et al.* (1970); Saario & Linnoila (1976); Zimmermann-Tansella *et al.* (1976)
	200	1	1	100	Malpas *et al.* (1970)
Butobarbitone	100	14	1	7	Adams (1974); Bond & Lader (1972); Peck *et al.* (1976); Walters & Lader (1971)
	150	7	1	14	Bond & Lader (1973)
	200	14	9	64	Adams (1974); Bond & Lader (1972); Peck *et al.* (1976); Walters & Lader (1971)
Heptabarbitone	200	1	1	100	Borland & Nicholson (1974)
	300	1	1	100	Borland & Nicholson (1974)
	400	1	1	100	Borland & Nicholson (1974)
Quinalbarbitone	100	5	0	0	Roth *et al.* (1979)
	200	5	1	20	Roth *et al.* (1979)
Secobarbital	100	15	1	7	Allnutt & O'Connor (1971); Bixler *et al.* (1979); Kaplan *et al.* (1968); Kornetsky *et al.* (1959); Roth *et al.* (1977, 1980b); Siegler *et al.* (1966)
	200	6	5	83	Kornetsky *et al.* (1959); Roth *et al.* (1980b)

Barbiturates: Insomniac Patients

Only two barbiturates, amylobarbitone (Hindmarch, 1979b; Malpas *et al.*, 1974; Tansella *et al.*, 1974) and amobarbital/secobarbital (Linnoila *et al.*, 1980), were used with insomniacs. Comparisons were made for 4 tasks: DSST, tracking, simple reaction time, and sorting. No decrements were reported.

Comparison of Task Sensitivity for Barbiturates and Benzodiazepines

The percent performance decrement, over all drugs and tasks in normal subjects for these two classes of drugs, was almost identical, 28.9% for benzodiazepines and 29.9% for the barbiturates. When tasks were ranked according to sensitivity, the rank-order correlation was positive (0.36), though not statistically significant. Of the 4 most sensitive tests for both drug classes, DSST and sorting rate were in both groups. Of the 4 least sensitive tasks, there were also 2 tasks common to both classes of drugs: rotary pursuit and Purdue Pegboard.

Other Sedative Hypnotics

In this group were chloral hydrate 1000 mg (Siegler, Winstin & Nodine, 1966), dichloralphenazone 325, 650 (Hindmarch & Parrott, 1980a), and 1300 mg (Hindmarch *et al.*, 1977b), ethchlorvynol 300 (Siegler *et al.*, 1966) and 500 mg (Kaplan, Forney, Hughes & Richards, 1968; Siegler *et al.*, 1966), glutethimide 250 (Saario & Linnoila, 1976) and 500 mg (Kaplan *et al.*, 1968; Siegler *et al.*, 1966), methaqualone 400 mg (Borland, Nicholson & Wright, 1975), methaqualone 250 mg with diphenhydramine 25 mg (Saario & Linnoila, 1976), and zopiclone 7.5 mg (Wickstrøm & Giercksky, 1980). As

indicated by the references, these drugs were used in few studies and only 10 of the tasks in Table 2 were used. None of these involved more than 4 placebo/drug comparisons. The total number of comparisons was 18, and 2 of these showed a decrement: simple reaction time with methaqualone 400 mg (Borland *et al.*, 1975) and pursuit rotor with glutethimide 500 mg (Siegler *et al.*, 1966).

Simulator Studies

Inferences to drug effects on real-life daily activities, from results of tests used in the laboratory, are often questioned. In an effort to make the laboratory studies more "realistic," simulators are often used. Flight simulator studies (Harper & Kidera, 1972; Hartman & McKenzie, 1966; McKenzie & Elliott, 1965) have primarily been done with barbiturates. Secobarbital 200 mg produced a significant decrement in performance 10 hours after ingestion (Hartman & McKenzie, 1966; McKenzie & Elliott, 1965), but a 100 mg dose level produced no significant effect (Hartman & McKenzie, 1966). Flurazepam 30 mg also produced no significant change in the simulated flight recorder data 12 hours after ingestion in a 2-night study (Harper & Kidera, 1972).

Simulator studies of automobile driving have also been reported (Hindmarch, Hanks & Hewett, 1977a; Saario *et al.*, 1975; Saario & Linnoila, 1976). Hindmarch *et al.* (1977a), in a 6-night study using clobazam 20 mg found no statistically significant effect when the drug and placebo data from their 10 subjects were compared. However, data from 2 subjects showed a marked decrement in both car driving ability and psychomotor performance after drug ingestion.

Though not revealing any statistical differences in objective scores of eye-hand coordination and psychomotor performance in a driving test, flurazepam 30 mg given at bedtime was related to more coordination errors in a driving test the next morning than found in subjects given 0.5 gm/kg alcohol 30, 60, or 90 minutes before the test (Saario *et al.*, 1975). In a second study (Saario & Linnoila, 1976), attention scores in a driving test were significantly impaired, but the coordination errors were not significantly different from chance.

DISCUSSION

Based on our analyses, the major conclusions are as follows:

1. Few sedative-hypnotic and performance studies have been done with insomniacs. Most studies have used young adult normal males.
2. Drug-related improvement in daytime performance was not found and, in comparing active drug to placebo, it is clear that all hypnotics (at some doses) produce decrements in performance the next day after nighttime ingestion.
3. The majority of the performance studies focused on psychomotor measures of performance. Little consistent data are available on cognitive functioning and more complex human behaviors.
4. Different psychomotor performance tests are differentially sensitive to the effects of sedative-hypnotics, and this pattern of sensitivity over tasks appears to be relatively similar for all types of sedative-hypnotics.
5. When multiple dose levels of a given drug were examined in a given study, consistent dose differences were found. High doses more consistently showed a decrement when compared with placebo performance than lower doses.
6. Although long-acting drugs generally show more performance decrement, the half-life data were not consistent.

Overall, our findings clearly indicate that taking any of the currently available sedative-hypnotics will not cause the next day's performance to excel over that when a placebo is taken. Sedative-hypnotics generally improve the quality of sleep, but not the quality of daytime performance. The higher doses are more likely to produce a performance decrement; thus, the physician should determine the lowest possible hypnotic dose for each patient.

Differential effects on performance. Upon examining the types of tasks used, it is clear that the researchers were concentrating on psychomotor tasks. Thus, any conclusions as to what specific abilities or functions are more or less likely to be impaired by sedative-hypnotics must be viewed against the abilities and functions measured by these 15 tests, or groups of tests. With this caveat in mind, one function appears to be most consistently impaired. That function is speed of performance. The 4 tests most sensitive to the benzodiazepines, and 3 of the 4 tests most sensitive to barbiturates, are heavily weighted on speed of performance. All the tasks also included a motor component, and performance on DSST, sorting, and cancellation have a cognitive component as well. But speed is the common denominator. As noted earlier, Wittenborn (1979), in his review, reported that the speed at which simple acts of a repetitive nature are performed was most likely to be impaired by benzodiazepines.

In contrast, the least sensitive tasks, coordination, CFF, and rotary pursuit, are not time-dependent. Arithmetic is more likely to show a decrement in the time domain; e.g., number of additions completed or time to complete serial subtraction, although number of errors may also be increased. It is not surprising that speed of performance would be most impaired. As Gilman, Goodman & Gilman (1980) note, "since most sedative-hypnotic drugs usually have the capability of producing widespread depression of the CNS, it is not surprising to find that CNS functions, in addition to the state of wakefulness, are usually depressed by these drugs" (p.339).

A finding not expected from the above reasoning was the consistent reports of anterograde amnesia following benzodiazepine use. The results of the three studies (Bixler *et al.*, 1979; Roth *et al.*, 1980b; Spinweber & Johnson, in press) were consistent in showing that information presented during the night following bedtime ingestion of a benzodiazepine was likely to be unavailable in the morning. Anterograde amnesia is well known, and, when the benzodiazepines are used intravenously as preoperation sedatives, it is viewed as a positive side-effect. It is, however, of concern when it appears following nighttime oral administration. It is unclear at this time what mechanisms cause this amnesic effect. Efforts are underway in the senior author's laboratory, as well as in Tom Roth's laboratory, and undoubtedly in others, to partial out the relative contribution of consolidations and retrieval factors in this memory problem.

No clear pattern of differential performance effects for classes of drugs or for specific drugs on the tests used in the 52 studies was evident. The overall percent decrement for the benzodiazepines and the barbiturates was similar, and the pattern from drug to drug was more alike than different.

Dose level, half-life and performance. An overview of all the sedative-hypnotics indicated that dose level was the most important factor in performance decrement. At the higher dose levels, all sedative-hypnotics were likely to be associated with impaired daytime performance. A discussion of dose level focuses on only one aspect of the important area of pharmacokinetics and

also raises the problem as to what dose level to recommend for efficacy. This review was not specifically directed toward efficacy or pharmacokinetics.

We had no data on drug absorption, distribution, or elimination. With respect to pharmacokinetics, however, we did take a broad look at the half-life of the benzodiazepines. We found that those benzodiazepines with longer half-lives of the parent compound (i.e., nitrazepam) or that of an active metabolite (i.e., flurazepam) had the higher percent decrements. The order of decrement for these two hypnotics, however, did not follow the length of their half-lives. Nitrazepam (with a reported half-life of 18–34 hours) always had a higher percent decrement than flurazepam, though the half-life of its metabolite is reported to be 24–100 hours (Gilman *et al.*, 1980). The testing times used by the studies reviewed invariably fell within the half-life period of both drugs.

The relation of half-life to performance is even less clear for sedative-hypnotics with shorter half-lives. One of the reasons for this lack of clarity is that few studies have been reported using these more recently introduced benzodiazepines. In addition to the small number of comparisons, the differing dose levels and the problem of comparability of the various dose levels must be kept in mind.

Nicholson (1981), while noting that hypnotics in which individual half-life did not exceed 24 hours are much less likely to lead to impaired performance, also observed that the persistence of residual sequelae may not relate as expected to elimination half-lives. Nicholson was referring particularly to diazepam in which he finds that ingestion of diazepam 5–10 mg overnight is uncomplicated by residual effects (Clarke & Nicholson, 1978). Diazepam has an elimination half-life of 14–90 hours.

Considering the importance of half-life and the concern over concentration of the drug in the body, one might have expected that there would have been numerous studies examining the relationship of serum levels of the sedative-hypnotics and performance. Few studies have been reported. In the one barbiturate study (Borland & Nicholson, 1974), the individual blood concentrations of heptabarbitone did not give a significant correlation with individual performance decrement. Linnoila *et al.* (1980) found a negative relationship between errors on a continuous tracking task, sleep duration, and N-desalkyl-flurazepam plasma levels. In two additional studies by this group (Saario *et al.*, 1975; Saario & Linnoila, 1976), there was no performance decrement over a 14-day period even though there was an increase in serum levels of nitrazepam, methaqualone, and N-desalkyl-flurazepam. Thus, there appears to be no linear relationship between drug levels in serum and performance. These serum level data are thus consistent with the finding that morning performance does not necessarily deteriorate following consecutive nights of administration.

With the general lack of a consistent relationship between performance and sedative-hypnotic serum levels, the question should be raised as to whether serum half-life is the most meaningful measure to use in predicting behavior. As we have noted, dose level--irrespective of the half-life of the particular agents--was the best predictor as to whether there would be a drug-induced performance deterioration in the morning. Plasma half-life per se, while important in metabolic-terms for pharmacokinetic descriptions, does not tell us the degree of CNS drug activity. The half-life simply tells us when half of the compound has disappeared from plasma. It is a mistake to extrapolate from this simple temporal descriptor that psychoactive effects will be present for

the duration of the half-life, or, for that matter, that psychoactive effects will be gone after the time corresponding to one half-life has passed.

For the study of the effects of hypnotics on performance, a new index--which we choose to call a behavioral index--is needed. This index would describe the effects of drugs in behavioral (i.e., performance) terms. For each drug, a performance curve from tests given at 1, 3, 5, 8, 12, 16, 20 hours post-ingestion would be developed on tasks that are known to be sensitive to that drug. The similarity of the performance decrement curve reported for triazolam by Spinweber & Johnson (in press) when sleeping subjects were awakened and by Nicholson & Stone (1980), in subjects who remained awake, suggests that whether the subject sleeps or remains awake may not be important. This curve should reflect the effect of dose level and the differential effect of use over nights, as well as sex and age. We believe that the mode and time course of elimination of the particular agent from the CNS would be more closely related to our behavioral index. Repeated measurement of performance effects to describe time course of action has only been done by a few investigators (Nicholson & Stone, 1980; Spinweber & Johnson, in press).

Related to dose level and half-life is the duration of the hangover effect the next day. Not surprising was the finding that for drugs with longer half-lives at the higher dose levels, the performance decrement was nearly constant over the 7 to 22.5 hour time period reviewed. But at high dose levels, in the few studies reported for shorter-acting benzodiazepines, performance decrement was also seen 12 to 22.5 hours post-ingestion.

An unexpected finding was that the largest decrement tended to occur during the middle of the day. This was particularly true for the lower dose levels. Upon reflection, this finding seems reasonable as there appears to be an interaction between the residual effects of sedative-hypnotics and the well known midday dip found in biological rhythms studies. This finding is of practical importance for sedative-hypnotic users who, after awakening feeling well rested, not being aware of this delayed midday effect, will be unprepared for, and probably unaware of, the larger than usual dip in their midday performance.

Dose level and efficacy. Both pharmaceutical companies and physicians face a complex problem: whether to recommend a dose level that insures rapid sleep onset and sustained sleep, but with a high probability of some performance decrement the next day, or to use a lower dose with a low probability of performance decrement but which may not improve sleep. Is an optimal balance possible? Again, our limited data do not permit a satisfactory answer. Since we question whether the normal subjects mostly used in performance studies are a satisfactory population to evaluate hypnotic efficacy, we have only the 8 studies that used insomniacs for our data base to make an efficacy evaluation. Only four of these used more than one dose level (Malpas *et al.*, 1974; Tansella *et al.*, 1974; Salkind & Silverstone, 1975; Hindmarch, 1979b). The results of these four studies for dose level and efficacy were inconsistent.

As another facet of his study, Hindmarch (1979b) addresses the question as to how the presentation of the hypnotic may influence efficacy and performance. He found that temazepam 20 mg in a Scherer capsule improved sleep quality with no morning hangover and contrasted this with the perceived hangover found following an acute dose of temazepam 20 mg in a conventional hard gelatin capsule. "When presented as a solution in a soft gelatin capsule, the maximal effect will be experienced more rapidly and the metabolic processes of elimination began almost immediately, so

making it possible for any residual effects to subside before the morning of the following day" (p.455).

Other unanswered questions. We note there are still little data as to effects of age, sex differences and, as decried in previous reviews, there are far too few performance studies using the medications on the population for which they are intended. Even fewer studies have attempted to determine the lowest effective dose level. Since over 20% of hypnotic prescriptions are written for the elderly patient, the paucity of studies with older insomniacs is a serious oversight. In a single study that compared young and elderly patients (Castleden *et al.*, 1977), nitrazepam 10 mg was found to produce significantly more mistakes on a psychomotor test, cancellation, in the elderly group, despite similar plasma concentrations of nitrazepam and half-lives in the two groups. The difference was thought to be due to the increased sensitivity of the aging brain to nitrazepam.

It is felt by some that the increased sleep time and improved quality of sleep will serve to cancel out any drug hangover effect. This reasoning leads to the hypothesis that there will be less performance decrement in insomniacs than in normals who do not have the benefit of more and better sleep. Due to the small number of insomniac studies, our results cannot provide a definitive answer, though the overall percent decrement for the insomniac test comparisons (18%) was smaller than the 29% for normals in the benzodiazepine studies. Another indication of the difference between normals and insomniacs can be obtained by examining the 9 tests that were given to both normals and insomniacs and in which both groups received flurazepam 30 mg. Of 22 comparisons, 27% showed a decrement in insomniacs, while 50% of 22 comparisons showed a decrement with normals.

A fundamental question, however, is: When compared to matched samples of noninsomniacs, is the daytime performance of unmedicated insomniacs impaired? The answer to this question is still unknown. Only one study (Church & Johnson, 1979) made a direct comparison of an untreated young adult group of poor sleepers, sleep onset insomniacs, with a matched sample of good sleepers. In this study, the early morning performance of the two groups did not differ on DSST, choice reaction time, and digit span. The only other study to address this question (Linnoila *et al.*, 1980) compared the tracking and reaction times of the insomniacs to those of normal subjects, who were administered the same tasks in a previous study, and noted that the baseline performance of the insomniac patients was poorer. Clearly, there needs to be more data to substantiate the concern of the insomniac that a "sleepless night" will lead to impaired performance the next day.

For many, the sleeping pill may not add more than a few minutes to their total night's sleep, but ingestion of the hypnotic abolishes their worries over not being able to sleep. As we are better able to classify the kinds of insomnia and types of patients, the physician will be able to more appropriately and selectively prescribe sleeping pills. The physician in most countries has a choice from very short-acting to long-acting hypnotics at various dose levels, with differing absorption, distribution, and elimination properties. Future research should provide data on the preferred type of hypnotic and dose level, along with the expected behavioral index for specific sleep complaints.

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(U) This paper reviews the published papers that involved presleep ingestion of hypnotics and administration of performance tasks the next day. To be included, studies had to have employed statistical analysis of drug vs. placebo performance and used a marketed hypnotic. Fifty-two studies met all criteria. The study subjects were primarily young noninsomniac males. Insomniacs were studied in only 8 studies. Eleven benzodiazepines, 7 barbiturates, and 7 "other" hypnotics were administered in one or more studies.

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20. ABSTRACT (continued)

The major conclusions are as follows:

1. Different performance tests are differentially sensitive to the effects of sedative-hypnotics, and this pattern of sensitivity over tasks appears to be relatively similar for all types of sedative-hypnotics.

2. The majority of the performance studies has focused on psychomotor measures of performance. Little consistent data are available on cognitive functioning and more complex human behaviors.

3. Drug-related improvement in daytime performance was not found and, in comparing active drug to placebo, it is clear that all hypnotics (at some doses) produce decrements in performance the next day after nighttime ingestion -- Because of the few studies reported, this conclusion is not as clear-cut in insomniacs as compared to normals.

4. When multiple dose levels of a given drug were examined in a given study, consistent dose differences were found. High doses more consistently showed a decrement when compared with placebo performance than lower doses.

5. The half-life data are less clear than those for dose level. Although long-acting drugs generally show more decrement, correlations between serum levels as measures of half-life and performance effects were not consistently found, but such data were rarely reported.

Overall, our findings clearly indicate that taking any of the currently available sedative-hypnotics will not cause the next day's performance to excel over that when a placebo is taken. Sedative-hypnotics generally improve the quality of sleep, but not the quality of daytime performance. Depending on the dose level, the price of "better" nighttime sleep may be poorer daytime performance.